



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/20, 31/40, 31/365, 31/22		A1	(11) International Publication Number: WO 99/30706 (43) International Publication Date: 24 June 1999 (24.06.99)
<p>(21) International Application Number: PCT/US98/23480</p> <p>(22) International Filing Date: 4 November 1998 (04.11.98)</p> <p>(30) Priority Data: 60/069,432 12 December 1997 (12.12.97) US</p> <p>(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): BISGAIER, Charles, Larry [US/US]; 3605 Tanglewood Drive, Ann Arbor, MI 48105 (US). NEWTON, Roger, Schofield [US/US]; 1425 Bardstown Trail, Ann Arbor, MI 48105 (US). RAMHARACK, Randy, Ranjee [CA/US]; 2465 Antietam Drive, Ann Arbor, MI 48105 (US).</p> <p>(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.</p>		<p>(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	
<p>(54) Title: ANTIHYPERLIPIDEMIC STATIN-LP(a) INHIBITOR COMBINATIONS</p> <p>(57) Abstract</p> <p>The invention is a pharmaceutical composition comprising an Lp(a) inhibitor and a statin which inhibits HMG-CoA reductase, said composition being useful for treating vascular diseases.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

ANTIHYPERLIPIDEMIC STATIN-LP(a) INHIBITOR COMBINATIONS

FIELD OF THE INVENTION

This invention concerns a combination of a statin compound, which is known to cause a reduction in plasma levels of low-density lipoproteins (LDL) cholesterol, and a compound which inhibits the formation of lipoprotein (a), Lp(a), which is a modified form of LDL, but which are unaffected by statins. The combination is useful for treating vascular disorders and diabetes mellitus.

BACKGROUND OF THE INVENTION

Several clinical studies have established that lowering certain forms of cholesterol in a mammal is an effective way to treat and prevent heart attacks, sudden death, and angina, both in subjects having higher than normal levels of circulating cholesterol, as well as those having normal levels of cholesterol. Lowering LDL, the bad form of cholesterol, is now one of the primary objectives of physicians treating patients who have, or who have a high risk of developing, cardiovascular diseases such as coronary heart disease, atherosclerosis, myocardial infarction, stroke, cerebral infarction, and even restenosis following balloon angioplasty. Many physicians are now utilizing cholesterol lowering agents purely as a prophylactic treatment in healthy subjects whose cholesterol levels are normal, thereby guarding against development of cardiovascular diseases.

The most commonly used cholesterol lowering agents are the statins, which are compounds which inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme responsible for catalyzing the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the cholesterol biosynthetic pathway.

There are several forms of circulating blood cholesterol which occur naturally in mammals. Some forms are considered "bad" cholesterol, while other forms are considered "good" cholesterol and are essential for good health. The

5

good form of cholesterol has been established to be high density lipoprotein (HDL). Low density lipoprotein (LDL) is a "bad" cholesterol. Another form of LDL cholesterol, the primary bad form, is a modified form of LDL called lipoprotein(a), or "Lp(a)". High levels of Lp(a) are now believed to be detrimental and can lead to cardiovascular diseases, and is one of the major risk factors leading to death from heart disease.

10

Because vascular diseases such as coronary heart disease, stroke, and even peripheral vascular disease, remain a leading cause of death and disability throughout the world, the need continues to develop new and improved treatments, as well as agents that will actually prevent the formation of these diseases.

15

We have now discovered that treatment and prevention of vascular diseases can be effected by administering a combination of a statin with an Lp(a) inhibitor. Typical Lp(a) inhibitors are the retinoids, as described in U.S. Patent 5,489,611 incorporated herein by reference.

SUMMARY OF THE INVENTION

20

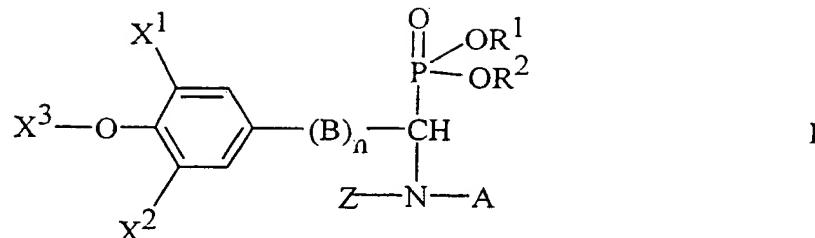
This invention provides a pharmaceutical composition comprised of an effective amount of a statin and an effective amount of an Lp(a) inhibitor. More particularly, one embodiment of the invention is a combination of a statin with an Lp(a) inhibitor which is a retinoid.

The combinations of this invention can also employ the pharmaceutically acceptable salts of the respective active components.

25

Preferred retinoids are those described in U.S. Patent 5,489,611. Especially preferred compositions employ 9-cis-retinoic acid or 13-cis-retinoic acid. Also preferred are trans-retinal and trans-retinol, as well as 13-cis-retinol, 13-cis-retinal, 9-cis-retinol, and 9-cis-retinal.

Another class of preferred Lp(a) inhibitors to be employed are aminophosphonates of the Formula I



wherein:

X^1 and X^2 independently are hydrogen, straight or branched C_1 - C_8 alkyl and C_1 - C_8 alkoxy, hydroxy, or nitro;

5 X^3 is hydrogen or C_1 - C_4 alkyl; or X^3O , together with one of X^1 or X^2 is an alkylidene dioxy ring having from 1 to 4 carbon atoms;

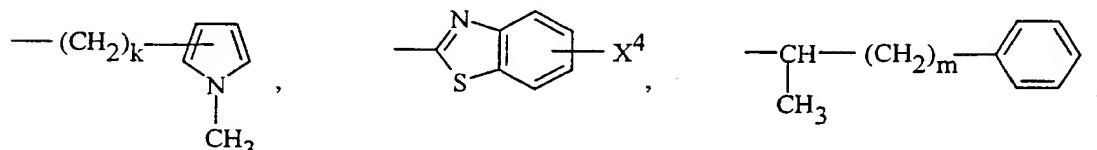
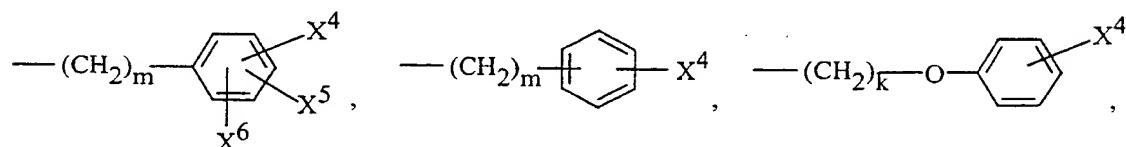
R^1 and R^2 independently are hydrogen, or straight or branched C_1 - C_6 alkyl;

B is CH_2 , $-CH_2CH_2-$, or $CH=CH-$;

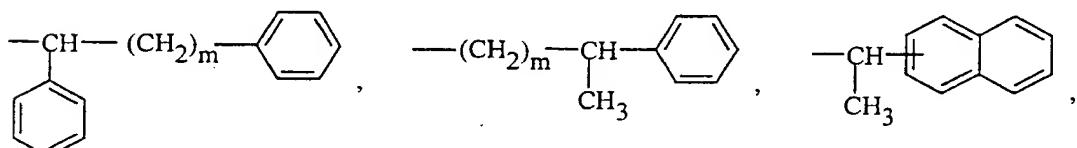
10 n is 0 or 1;

Z is hydrogen, straight or branched C_1 - C_8 alkyl, an aryl group Ar , or R^3CO , where R^3 is C_1 - C_4 alkyl or perfluoro C_1 - C_4 alkyl;

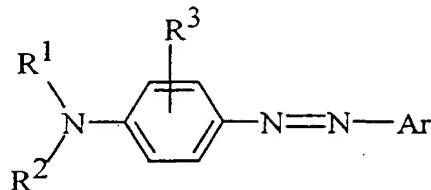
A is hydrogen, $CH_2CH=CH_2$, straight or branched C_1 - C_8 alkyl or



15



-5-



III

where

R¹ and R² independently are hydrogen or straight or branched C₁-C₆ alkyl, or taken together with the nitrogen to which they are attached complete a 5- to 7-membered ring, optionally substituted with C₁-C₆ alkyl or C₁-C₆ alkoxy;

R³ is C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, halo, nitro, perfluoroalkyl, amino, C₁-C₆ alkyl or di-C₁-C₆ alkyl amino, or cyano; and

Ar is phenyl optionally substituted by carboxyl, C₁-C₆ alkoxy carbonyl, cyano, CONH₂, SO₂NH₂, C₁-C₆ alkyl, C₁-C₆ alkoxy, hydroxy, halo, nitro, amino, C₁-C₆ alkyl or di-C₁-C₆ alkyl amino, or C₁-C₆ aryl amino.

The compositions preferably will contain compounds of Formula III such as:

- 4-[(4-(N,N-diethylamino)phenyl)azo]-benzonitrile;
- 4-[(2-Chloro-4-N,N-dimethylamino)phenyl]azo]-benzonitrile;
- 15 4-[(4-(N,N-diethylamino)phenyl)azo]-benzoic acid ethyl ester;
- 3-[(4-(N-piperidyl)phenyl)azo]-benzonitrile;
- 4-[(4-(N,N-dimethylamino)phenyl)azo]-benzamide; and
- 4-[(4-(N,N-dimethylamino)phenyl)azo]-benzsulfonamide.

Such phenylazo compounds are described in U.S. Patent 4,397,944, 3,978,201, 20 and in WO 97/26890, all incorporated herein by reference.

Typical statins to be employed in combination with the compound of Formula I include atorvastatin, simvastatin, pravastatin, cerivastatin, mevastatin, velostatin, fluvastatin, lovastatin, dalvastatin, and fluindostatin. The statins can be employed as pharmaceutically acceptable salts, for example, atorvastatin calcium.

25 A particularly preferred composition of this invention utilizes a retinoid together with a statin selected from atorvastatin calcium, pravastatin sodium,

simvastatin, lovastatin, and cerivastatin. The most preferred composition employs the compound of Formula III with atorvastatin calcium.

Also provided by the invention are methods for treating vascular diseases such as peripheral vascular disease, coronary heart disease, stroke, and restenosis.

5 The invention provides a method for lowering Lp(a), plasma triglycerides, very low-density lipoprotein (VLDL) cholesterol, LDL cholesterol, and apolipoprotein B. The invention additionally provides a method for elevating plasma HDL cholesterol, apolipoprotein A-I, and apolipoprotein E. The invention also provides a method for treating and preventing noninsulin-dependent diabetes 10 mellitus by increasing insulin sensitivity comprising administering a combination of this invention.

DETAILED DESCRIPTION OF THE INVENTION

We have discovered that combining a statin with an Lp(a) inhibitor provides a surprisingly effective composition for treating and preventing vascular 15 diseases, as well as diabetes mellitus. An Lp(a) inhibitor is any compound which is effective at reducing Lp(a) in a mammal. As noted above, the Lp(a) inhibitors as used herein are compounds such as those described in U.S. Patent 5,489,611 and 5,424,303, both incorporated herein by reference. The compounds can be the free acid or a salt form.

20 The other active component of the combinations of this invention is a statin. The term "statin", where used in the specification and the appendant claims, is synonymous with the terms "3-hydroxy-3-methylglutaryl-Coenzyme A reductase inhibitor" and "HMG-CoA reductase inhibitor." These three terms are used interchangeably throughout the specification and appendant claims. As the 25 synonyms suggest, statins are inhibitors of 3-hydroxy-3-methylglutaryl-Coenzyme A reductase and, as such, are effective in lowering the level of blood plasma cholesterol. Statins and pharmaceutically acceptable salts thereof are particularly useful in lowering low-density lipoprotein cholesterol (LDL-C) levels in mammals, and particularly in humans.

The HMG-CoA reductase inhibitors suitable for use herein include, but are not limited to, simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, cerivastatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, or lovastatin; or a pharmaceutically acceptable salt of simvastatin, pravastatin, rivastatin, cerivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, lovastatin, or pharmaceutically acceptable salts thereof. However, it is to be noted that atorvastatin calcium is a particularly preferred statin to be employed in the present combination. See U.S. Patent 5,273,995 incorporated herein by reference.

The statins disclosed herein are prepared by methods well-known to those skilled in the art. Specifically, simvastatin may be prepared according to the method disclosed in U.S. Patent 4,444,784, which is incorporated herein by reference. Pravastatin may be prepared according to the method disclosed in U.S. Patent 4,346,227, which is incorporated herein by reference. Cerivastatin may be prepared according to the method disclosed in U.S. Patent 5,502,199, which is incorporated herein by reference. Cerivastatin may alternatively be prepared according to the method disclosed in European Patent Application Publication No. EP617019. Mevastatin may be prepared according to the method disclosed in U.S. Patent 3,983,140, which is incorporated herein by reference. Velostatin may be prepared according to the methods disclosed in U.S. Patent 4,448,784 and U.S. Patent 4,450,171, both of which are incorporated herein by reference. Fluvastatin may be prepared according to the method disclosed in U.S. Patent 4,739,073, which is incorporated herein by reference. Compactin may be prepared according to the method disclosed in U.S. Patent 4,804,770, which is incorporated herein by reference. Lovastatin may be prepared according to the method disclosed in U.S. Patent 4,231,938, which is incorporated herein by reference. Dalvastatin may be prepared according to the method disclosed in European Patent Application Publication No. 738510 A2. Fluindostatin may be prepared according to the method disclosed in European Patent Application Publication No. 363934 A1. Dihydrocompactin may be prepared according to the method disclosed in U.S. Patent 4,450,171, which is incorporated herein by reference.

It will be recognized that certain of the above statins contain either a free carboxylic acid or a free amine group as part of the chemical structure. Further,

certain statins within the scope of this invention contain lactone moieties, which exist in equilibrium with the free carboxylic acid form. These lactones can be maintained as carboxylates by preparing pharmaceutically acceptable salts of the lactone. Thus, this invention includes pharmaceutically acceptable salts of those carboxylic acids or amine groups. The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically acceptable cationic salts" is intended to define but is not limited to such salts as the alkali metal salts, (e.g., sodium and potassium), alkaline earth metal salts (e.g., calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically acceptable add addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

The pharmaceutically acceptable cationic salts of statins containing free carboxylic acids may be readily prepared by reacting the free acid form of the statin with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine, and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt of the cation (sodium or potassium ethylhexanoate, magnesium oleate), employing a solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent.

The pharmaceutically acceptable acid addition salts of statins containing free amine groups may be readily prepared by reacting the free base form of the

statin with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate), or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at 5 least one molar equivalent and usually a molar excess of the acid is employed. However, when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate, or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be 10 otherwise isolated by concentration and/or addition of a non-solvent.

Further, the statins of the instant invention and the pharmaceutically acceptable salts of the statins of the instant invention may also occur as hydrates or solvates. Said hydrates and solvates are also within the scope of the invention. The same holds true for the Lp(a) inhibitors, for example, the retinoids.

15 The pharmaceutical combinations and methods of this invention are all adapted to therapeutic use as agents in the prevention and treatment of atherosclerosis, angina pectoris, and a condition characterized by the presence of both hypertension and hyperlipidemia in mammals, particularly humans. Further, since these diseases and conditions are closely related to the development of 20 cardiac disease and adverse cardiac conditions, these combinations and methods, by virtue of their action as antiatherosclerotics, antianginals, antihypertensives, and antihyperlipidemics are useful in the management of cardiac risk in subjects at risk of developing adverse cardiac conditions and in subjects at risk of suffering adverse cardiac events.

25 The utility of the compositions of the present invention as medical agents in the treatment of atherosclerosis in mammals (e.g., humans) is demonstrated by the activity of the compounds of this invention in conventional assays and in a clinical protocol such as that described below.

Effect of an Lp(a) Inhibitor and a Statin, Alone and in Combination,
on the Treatment of Atherosclerosis

This study is a prospective randomized evaluation of the effect of a combination of 9-cis-retinoic acid or a pharmaceutically acceptable salt thereof and a statin on the progression/regression of coronary and carotid artery disease. The study is used to show that a combination of 9-cis-retinoic acid or a pharmaceutically acceptable acid addition salt and a statin is effective in slowing or arresting the progression or causing regression of existing coronary artery disease (CAD) as evidenced by changes in coronary angiography or carotid ultrasound, in subjects with established disease.

This study is an angiographic documentation of coronary artery disease carried out as a double-blind, placebo-controlled trial of a minimum of about 500 subjects and preferably of about 780 to about 1200 subjects. It is especially preferred to study about 1200 subjects in this study. Subjects are admitted into the study after satisfying certain entry criteria set forth below.

Entry criteria: Subjects accepted for entry into this trial must satisfy certain criteria. Thus, the subject must be an adult, either male or female, aged 18 to 80 years of age in whom coronary angiography is clinically indicated. Subjects will have angiographic presence of a significant focal lesion such as 30% to 50% on subsequent evaluation by quantitative coronary angiography (QCA) in a minimum of one segment (non-PTCA, non-bypassed, or non-MI vessel) that is judged not likely to require intervention over the next 3 years. It is required that the segments undergoing analysis have not been interfered with. Since percutaneous transluminal cardiac angioplasty (PTCA) interferes with segments by the insertion of a balloon catheter, non-PTCA segments are required for analysis. It is also required that the segments to be analyzed have not suffered a thrombotic event, such as a myocardial infarct (MI). Thus, the requirement for non-MI vessels. Segments that will be analyzed include: left main, proximal, mid and distal left anterior descending, first and second diagonal branch, proximal and distal left circumflex, first or largest space obtuse marginal, proximal, mid and distal right coronary artery. Subjects will have an ejection fraction of greater than 30% determined by catheterization or radionuclide ventriculography or ECHO

cardiogram at the time of the qualifying angiogram or within the previous 3 months of the acceptance of the qualifying angiogram provided no intervening event such as a thrombotic event or procedure such as PTCA has occurred.

Generally, due to the number of patients and the physical limitations of any one facility, the study is carried out at multiple sites. At entry into the study, subjects undergo quantitative coronary angiography as well as B-mode carotid artery ultrasonography and assessment of carotid arterial compliance at designated testing centers. This establishes baselines for each subject. Once admitted into the test, subjects are randomized to receive the compound of 9-cis-retinoic acid (200 mg) and placebo or a statin (dose is dependent upon the particular statin used; however, generally 80 mg will be used at first) and placebo or 9-cis-retinoic acid (200 mg) and a statin (80 mg). It will be recognized by a skilled person that the free base form or other salt forms of 9-cis-retinoic acid or the free base form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statin and 9-cis-retinoic acid is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved. The amount of 9-cis-retinoic acid may be varied as required. Generally, a subject will start out taking 200 mg, and the amount will be titrated down to as little as 50 mg as determined by the clinical physician. The amount of the statin will similarly be titrated down from 80 mg if it is determined by the physician to be in the best interests of the subject. The subjects are monitored for a 1- to 3-year period, generally 3 years being preferred. B-mode carotid ultrasound assessment of carotid artery atherosclerosis and compliance are performed at regular intervals throughout the study.

Generally, 6-month intervals are suitable. Typically this assessment is performed using B-mode ultrasound equipment. However, a person skilled in the art may use other methods of performing this assessment. Coronary angiography is performed at the conclusion of the 1- to 3-year treatment period. The baseline and posttreatment angiograms and the intervening carotid artery B-mode ultrasonograms are evaluated for new lesions or progression of existing atherosclerotic lesions. Arterial compliance measurements are assessed for changes from baseline and over the 6-month evaluation periods.

The primary objective of this study is to show that the combination of carboxyalkylether or a pharmaceutically acceptable acid addition salt and a statin reduces the progression of atherosclerotic lesions as measured by quantitative coronary angiography (QCA) in subjects with clinical coronary artery disease.

5 QCA measures the opening in the lumen of the arteries measured.

The primary endpoint of the study is the change in the average mean segment diameter of the coronary artery tree. Thus, the diameter of an arterial segment is measured at various portions along the length of that segment. The average diameter of that segment is then determined. After the average segment diameter of many segments has been determined, the average of all segment averages is determined to arrive at the average mean segment diameter. The mean segment diameter of subjects taking a statin and 9-cis-retinoic acid or a pharmaceutically acceptable acid addition salt will decline more slowly, will be halted completely, or there will be an increase in the mean segment diameter.

10 15 These results represent slowed progression of atherosclerosis, no change in the progression of atherosclerosis, and regression of atherosclerosis, respectively.

The secondary objective of this study is that the combination of carboxyalkylether or a pharmaceutically acceptable acid addition salt and a statin reduces the rate of progression of atherosclerosis in the carotid arteries as measured by the slope of the maximum intimal-medial thickness measurements averaged over 12 separate wall segments (Mean Max) as a function of time, more than does compound III or a pharmaceutically acceptable acid addition salt or a statin alone. The intimal-medial thickness of subjects taking a statin and compound III or a pharmaceutically acceptable salt thereof will increase more slowly, will cease to increase, or will decrease. These results represent slowed progression of atherosclerosis, halted progression of atherosclerosis, and regression of atherosclerosis, respectively. Further, these results may be used to facilitate dosage determinations.

20 25 30 The utility of the compounds of the present invention as medical agents in the treatment of angina pectoris in mammals (e.g., humans) is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below.

Effect of 9-Cis-Retinoic Acid and a Statin, Alone and in Combination,
on the Treatment of Angina

5 This study is a double-blind, parallel-arm, randomized study to show the effectiveness of 9-cis-retinoic acid or a pharmaceutically acceptable acid addition salt thereof and a statin given in combination in the treatment of symptomatic angina.

10 *Entry criteria:* Subjects are males or females between 18 and 80 years of age with a history of typical chest pain associated with one of the following objective evidences of cardiac ischemia: (1) stress test segment elevation of about one millimeter or more from the ECG; (2) positive treadmill stress test; (3) new wall motion abnormality on ultrasound; or (4) coronary angiogram with a significant qualifying stenosis. Generally a stenosis of about 30% to 50% is considered to be significant.

15 Each subject is evaluated for about 10 to 32 weeks. At least 10 weeks are generally required to complete the study. Sufficient subjects are used in this screen to ensure that about 200 to 800 subjects and preferably about 400 subjects are evaluated to complete the study. Subjects are screened for compliance with the entry criteria, set forth below, during a 4-week run-in phase. After the screening criteria are met, subjects are washed out from their current anti-anginal medication 20 and stabilized on a long acting nitrate such as nitroglycerine, isosorbide-5-mononitrate or isosorbide dinitrate. The term "washed out", when used in connection with this screen, means the withdrawal of current anti-anginal medication so that substantially all of said medication is eliminated from the body of the subject. A period of 8 weeks is preferably allowed for both the washout 25 period and for the establishment of the subject on stable doses of said nitrate. Subjects having one or two attacks of angina per week while on stable doses of long acting nitrate are generally permitted to skip the washout phase. After subjects are stabilized on nitrates, the subjects enter the randomization phase provided the subjects continue to have either one or two angina attacks per week. 30 In the randomization phase, the subjects are randomly placed into one of the four arms of the study set forth below. After completing the washout phase, subjects in compliance with the entry criteria undergo 24-hour ambulatory electrocardiogram

5

(ECG) such as Holter monitoring, exercise stress testing such as a treadmill, and evaluation of myocardial perfusion using photon emission tomography (PET) scanning to establish a baseline for each subject. When conducting a stress test, the speed of the treadmill and the gradient of the treadmill can be controlled by a technician. The speed of the treadmill and the angle of the gradient are generally increased during the test. The time intervals between each speed and gradient increase is generally determined using a modified Bruce Protocol.

10

After the baseline investigations have been completed, subjects are initiated on one of the following four arms of the study: (1) placebo; (2) a statin (about 2.5 mg to about 160 mg); (3) 9-cis-retinoic acid (about 25 mg to about 200 mg); or (4) a combination of the above doses of 9-cis-retinoic acid and a statin together. The subjects are then monitored for 2 to 24 weeks. It will be recognized by a skilled person that the free base form or other salt forms of compound III or the free base form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statin and compound III is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

15

After the monitoring period has ended, subjects will undergo the following investigations: (1) 24-hour ambulatory ECG, such as Holter monitoring; (2) exercise stress testing (e.g., treadmill using said modified Bruce Protocol); and (3) evaluation of myocardial perfusion using PET scanning. Patients keep a diary of painful ischemic events and nitroglycerine consumption. It is generally desirable to have an accurate record of the number of anginal attacks suffered by the patient during the duration of the test. Since a patient generally takes nitroglycerin to ease the pain of an anginal attack, the number of times that the patient administers nitroglycerine provides a reasonably accurate record of the number of anginal attacks.

25

To demonstrate the effectiveness and dosage of the drug combination of this invention, the person conducting the test will evaluate the subject using the tests described. Successful treatment will yield fewer instances of ischemic events as detected by ECG, will allow the subject to exercise longer or at a higher intensity level on the treadmill or to exercise without pain on the treadmill, or will yield better perfusion or fewer perfusion defects on PET.

The utility of the compounds of the present invention as medical agents in the treatment of hypertension and hyperlipidemia in mammals (e.g., humans) suffering from a combination of hypertension and hyperlipidemia is demonstrated by the activity of the compounds of this invention in conventional assays and the 5 clinical protocol described below.

Effects of an Lp(a) Inhibitor and a Statin, Alone and in Combination, on the Treatment of Subjects Having Both Hypertension and Hyperlipidemia

This study is a double-blind, parallel-arm, randomized study to show the effectiveness of carboxyalkylether or a pharmaceutically acceptable acid addition 10 salt thereof and a statin given in combination in controlling both hypertension and hyperlipidemia in subjects who have mild, moderate, or severe hypertension and hyperlipidemia.

Each subject is evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are used in this screen to ensure that about 400 to 800 subjects 15 are evaluated to complete the study.

Entry criteria: Subjects are male or female adults between 18 and 80 years of age having both hyperlipidemia and hypertension. The presence of hyperlipidemia is evidenced by evaluation of the LDL cholesterol level of the 20 subject relative to certain positive risk factors. If the subject has no coronary heart disease (CHD) and has less than two positive risk factors, then the subject is considered to have hyperlipidemia, which requires drug therapy if the LDL of the subject is ≥ 190 mg/dL. If the subject has no CHD and has two or more positive risk factors, then the subject is considered to have hyperlipidemia, which requires drug therapy if the LDL of the subject is ≥ 160 mg/dL. If the subject has CHD, 25 then the subject is considered to have hyperlipidemia if the LDL of the subject is ≥ 130 mg/dL.

Positive risk factors include: (1) male over 45, (2) female over 55 wherein said female is not undergoing hormone replacement therapy (HRT), (3) family history of premature cardiovascular disease, (4) the subject is a current smoker, 30 (5) the subject has diabetes, (6) an HDL of less than 45 mg/dL, and (7) the subject

has hypertension. An HDL of >60 mg/dL is considered a negative risk factor and will offset one of the above mentioned positive risk factors.

5 The presence of hypertension is evidenced by a sitting diastolic blood pressure (BP) of >90 mmHg or sitting systolic BP of >140 mmHg. All blood pressures are generally determined as the average of three measurements taken 5 minutes apart.

10 Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, subjects are washed out from their current antihypertensive and lipid lowering medication and are placed on the NCEP ATP II Step 1 diet. The NCEP ATP II (adult treatment panel, 2nd revision) Step 1 diet sets forth the amount of saturated and unsaturated fat which can be consumed as a proportion of the total caloric intake. The term "washed out", where used in connection with this screen, means the withdrawal of current antihypertensive and lipid lowering medication so that substantially all of said 15 medication is eliminated from the body of the subject. Newly diagnosed subjects generally remain untreated until the test begins. These subjects are also placed on the NCEP Step 1 diet. After the 4-week washout and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure and (2) fasting lipid screen. The fasting lipid screen determines baseline lipid levels in 20 the fasting state of a subject. Generally, the subject abstains from food for 12 hours, at which time lipid levels are measured.

25 After the baseline investigations are performed, subjects are started on one of the following: (1) a fixed dose of 9-cis-retinoic acid, generally about 25 to 200 mg; (2) a fixed dose of a statin, generally about 2.5 mg to about 160 mg; or (3) a combination of the above doses of 9-cis-retinoic acid and a statin together. It will be recognized by a skilled person that the free base form or other salt forms of 9-cis-retinoic acid or the free base form or other salt forms of the statin may be used in this invention. Calculation of the dosage amount for these other forms of the statin and 9-cis-retinoic acid is easily accomplished by performing a simple 30 ratio relative to the molecular weights of the species involved. Subjects remain on these doses for a minimum of 6 weeks, and generally for no more than 8 weeks. The subjects return to the testing center at the conclusion of the 6 to 8 weeks so that the baseline evaluations can be repeated. The blood pressure of the subject at

the conclusion of the study is compared with the blood pressure of the subject upon entry. The lipid screen measures the total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, apoB, very low-density lipoprotein (VLDL) and other components of the lipid profile of the subject. Improvements in the values obtained after treatment relative to pretreatment values indicate the utility of the drug combination.

The utility of the compounds of the present invention as medical agents in the management of cardiac risk in mammals (e.g., humans) at risk for an adverse cardiac event is demonstrated by the activity of the compounds of this invention in conventional assays and the clinical protocol described below.

Effects of an Lp(a) Inhibitor and a Statin, Alone and in Combination,
on Subjects at Risk of Future Cardiovascular Events

This study is a double-blind, parallel-arm, randomized study to demonstrate the effectiveness of carboxyalkylether or a pharmaceutically acceptable acid addition salt and a statin given in combination in reducing the overall calculated risk of future events in subjects who are at risk for having future cardiovascular events. This risk is calculated by using the Framingham Risk Equation. A subject is considered to be at risk of having a future cardiovascular event if that subject is more than one standard deviation above the mean as calculated by the Framingham Risk Equation. The study is used to evaluate the efficacy of a fixed combination of carboxylalkylether or a pharmaceutically acceptable acid addition salt and a statin in controlling cardiovascular risk by controlling both hypertension and hyperlipidemia in patients who have both mild to moderate hypertension and hyperlipidemia.

Each subject is evaluated for 10 to 20 weeks and preferably for 14 weeks. Sufficient subjects are recruited to ensure that about 400 to 800 subjects are evaluated to complete the study.

Entry criteria: Subjects included in the study are male or female adult subjects between 18 and 80 years of age with a baseline 5-year risk, which risk is above the median for said subject's age and sex, as defined by the Framingham Heart Study, which is an ongoing prospective study of adult men and women

showing that certain risk factors can be used to predict the development of coronary heart disease. The age, sex, systolic and diastolic blood pressure, smoking habit, presence or absence of carbohydrate intolerance, presence or absence of left ventricular hypertrophy, serum cholesterol, and HDL of more than 5 one standard deviation above the norm for the Framingham Population are all evaluated in determining whether a patient is at risk for adverse cardiac event. The values for the risk factors are inserted into the Framingham Risk Equation and calculated to determine whether a subject is at risk for a future cardiovascular event.

10 Subjects are screened for compliance with the entry criteria set forth above. After all screening criteria are met, patients are washed out from their current antihypertensive and lipid lowering medication and any other medication which will impact the results of the screen. The patients are then placed on the NCEP ATP II Step 1 diet, as described above. Newly diagnosed subjects generally 15 remain untreated until the test begins. These subjects are also placed on the NCEP ATP II Step 1 diet. After the 4-week washout and diet stabilization period, subjects undergo the following baseline investigations: (1) blood pressure; (2) fasting; (3) lipid screen; (4) glucose tolerance test; (5) ECG; and (6) cardiac ultrasound. These tests are carried out using standard procedures well-known to 20 persons skilled in the art. The ECG and the cardiac ultrasound are generally used to measure the presence or absence of left ventricular hypertrophy.

25 After the baseline investigations are performed, patients will be started on one of the following: (1) a fixed dose of 9-cis-retinoic acid (about 25 to 200 mg); (2) a fixed dose of a statin (about 2.5 mg to about 160 mg); or (3) the combination of the above doses of 9-cis-retinoic acid and a statin. Patients are kept on these doses and are asked to return in 6 to 8 weeks so that the baseline evaluations can be repeated. At this time, the new values are entered into the Framingham Risk Equation to determine whether the subject has a lower, greater, or no change in the risk of future cardiovascular event.

30 The above assays demonstrating the effectiveness of a retinoid or pharmaceutically acceptable acid addition salts thereof and atorvastatin or pharmaceutically acceptable salts thereof in the treatment of angina pectoris, atherosclerosis, hypertension and hyperlipidemia together, and the management of

cardiac risk, also provide a means whereby the activities of the compounds of this invention can be compared between themselves and with the activities of other known compounds. The results of these comparisons are useful for determining synergistic dosage levels in mammals, including humans, for the treatment of such diseases.

The following dosage amounts and other dosage amounts set forth elsewhere in this specification and in the appendant claims are for an average human subject having a weight of about 65 kg to about 70 g. The skilled practitioner will readily be able to determine the dosage amount required for a subject whose weight falls outside the 65 to 70 kg range, based upon the medical history of the subject and the presence of diseases, e.g., diabetes, in the subject. All doses set forth herein, and in the appendant claims, are daily doses.

In general, in accordance with this invention, the Lp(a) inhibitor is generally administered in a dosage of about 25 mg to about 500 mg. Preferably, 9-cis-retinoic acid is administered in a dosage of about 5 mg to about 100 mg. It will be recognized by a skilled person that the free base form or other salt forms of 9-cis-retinoic acid may be used in this invention. Calculation of the dosage amount for these other forms of or the free base form or other salt forms of La(a) inhibitors is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

In general, in accordance with this invention, the above statins are administered in the following dosage amounts:

Simvastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg;

Pravastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg;

Cerivastatin, generally about 25 µg to about 5 mg and preferably about 1 mg to about 3.2 mg;

Fluvastatin, generally about 2.5 mg to about 160 mg and preferably about 20 mg to about 80 mg;

Lovastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 80 mg; and

l

Atorvastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 80 mg.

It will be recognized by a skilled person that the free base form or other salt forms of the above statins may be used in this invention. Calculation of the dosage amount for these other forms of or the free base form or other salt forms said statins is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

The compounds of the present invention are generally administered in the form of a pharmaceutical composition comprising at least one of the compounds of this invention together with a pharmaceutically acceptable carrier or diluent. Thus, the compounds of this invention can be administered either individually or together in any conventional oral, parenteral, or transdermal dosage form.

For oral administration, a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate, and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin, and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate, and talc are often very useful for tableting purposes. Solid compositions of a similar type are also employed as fillers in soft- and hard-filled gelatin capsules; preferred materials in this connection also include lactose or milk sugar, as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the compounds of this invention can be combined with various sweetening agents, flavoring agents, coloring agents, emulsifying agents, and/or suspending agents, as well as such diluents as water, ethanol, propylene glycol, glycerin, and various like combinations thereof.

The combinations of this invention may also be administered in a controlled release formulation such as a slow release or a fast release formulation. Such controlled release formulations of the combination of this invention may be prepared using methods well-known to those skilled in the art. The method of administration will be determined by the attendant physician or other person skilled in the art after an evaluation of the subject's condition and requirements.

The generally preferred formulation of atorvastatin calcium is Lipitor® as described in U.S. Patent 5,686,104, incorporated herein by reference.

For purposes of parenteral administration, solutions in sesame or peanut oil or in aqueous propylene glycol can be employed, as well as sterile aqueous 5 solutions of the corresponding water-soluble salts. Such aqueous solutions may be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous, and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are all readily obtainable 10 by standard techniques well-known to those skilled in the art.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples, see *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easter, Pennsylvania., 15th 15 Edition (1975).

Pharmaceutical compositions according to the invention may contain 0.1% to 95% of the compound(s) of this invention, preferably 1% to 70%. In any event, the composition or formulation to be administered will contain a quantity of a compound(s) according to the invention in an amount effective to treat the 20 condition or disease of the subject being treated.

Since the present invention relates to the treatment of diseases and conditions with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit includes two separate pharmaceutical 25 compositions: a carboxyalkylether or a pharmaceutically acceptable acid addition salt thereof and a statin or a pharmaceutically acceptable salt thereof. The kit includes container means for containing the separate compositions such as a divided bottle or a divided foil packet; however, the separate compositions may also be contained within a single, undivided container. Typically, the kit includes 30 directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered

-22-

at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

It should be understood that the invention is not limited to the particular embodiments described herein, but that various changes and modifications may be made without departing from the spirit and scope of this novel concept as defined by the following claims.

5

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising:
 - a. an amount of an Lp(a) inhibitor or a pharmaceutically acceptable salt thereof;
 - b. an amount of a statin or a pharmaceutically acceptable salt thereof; and
 - c. a pharmaceutically acceptable carrier or diluent.
2. A pharmaceutical composition of Claim 1 wherein said statin is atorvastatin, simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, cerivastatin, or lovastatin; or a pharmaceutically acceptable salt thereof.
3. A pharmaceutical composition of Claim 2 wherein said statin is atorvastatin, simvastatin, pravastatin, mevastatin, lovastatin, cerivastatin, or pharmaceutically acceptable salts thereof.
4. A pharmaceutical composition of Claim 3 wherein the Lp(a) inhibitor is a retinoid.
5. A pharmaceutical composition of Claim 4 comprising atorvastatin calcium and 9-cis-retinoic acid.
- 20 6. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a hypolipidemic effect in a mammal suffering from hyperlipidemia, which effects are greater than the sum of the hypolipidemic effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of an Lp(a) inhibitor or a pharmaceutically acceptable acid addition salt thereof and a

5 pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent; provided that said statin is not atorvastatin or a pharmaceutically acceptable salt thereof.

10 7. A composition of Claim 6 wherein said statin is atorvastatin, simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, cerivastatin, or lovastatin; or a pharmaceutically acceptable salt of simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, cerivastatin, or lovastatin.

15 8. A composition of Claim 7 wherein said second pharmaceutical composition comprises a retinoid.

20 9. A first pharmaceutical composition for use with a second pharmaceutical composition for achieving a hypolipidemic effect in a mammal suffering from hyperlipidemia, which effects are greater than the sum of the hypolipidemic effects achieved by administering said first and second pharmaceutical compositions separately and which second pharmaceutical composition comprises an amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of 9-cis-retinoic acid.

25 10. A composition of Claim 9 wherein said statin is atorvastatin, simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, cerivastatin, or lovastatin; or a pharmaceutically acceptable salt thereof.

11. A composition of Claim 10 comprising 9-cis-retinoic acid.

12. A first pharmaceutical composition for use with a second pharmaceutical composition for managing cardiac risk in a mammal at risk of suffering an adverse cardiac event, which effect is greater than the sum of the cardiac risk management effects achieved by administering said first and second pharmaceutical compositions separately, and which second pharmaceutical composition comprises an amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent, said first pharmaceutical composition comprising an amount of an Lp(a) inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

13. A composition of Claim 12 wherein said statin is atorvastatin, simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, cerivastatin, or lovastatin; or a pharmaceutically acceptable salt of simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, or lovastatin.

14. A composition of Claim 13 comprising a retinoid.

15. A kit for achieving a therapeutic effect in a mammal comprising:

- an amount of an Lp(a) inhibitor or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a first unit dosage form;
- an amount of a statin or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent in a second unit dosage form; and
- container means for containing said first and second dosage forms; provided that said statin is not atorvastatin or a pharmaceutically acceptable salt thereof.

16. A kit of Claim 15 wherein said statin is atorvastatin, simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin,

dalvastatin, dihydrocompactin, compactin, cerivastatin, or lovastatin; or a pharmaceutically acceptable salt of simvastatin, pravastatin, rivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, cerivastatin, or lovastatin.

- 5 17. A kit of Claim 16 comprising a retinoid.
18. A kit of Claim 17 employing 9-cis-retinoic acid.
19. A kit of Claim 15 wherein said therapeutic effect is treatment of hyperlipidemia.
20. A kit of Claim 15 wherein said therapeutic effect is treatment of angina pectoris.
- 10 21. A kit of Claim 15 wherein said therapeutic effect is treatment of cardiac risk.
22. A kit of Claim 15 wherein said therapeutic effect is treatment of atherosclerosis.
- 15 23. A kit of Claim 22 wherein said treatment of atherosclerosis slows the progression of atherosclerotic plaques.
24. A kit of Claim 23 wherein said progression of atherosclerotic plaques is slowed in coronary arteries.
- 20 25. A kit of Claim 23 wherein said progression of atherosclerotic plaques is slowed in carotid arteries.
26. A kit of Claim 23 wherein said progression of atherosclerotic plaques is slowed in the peripheral arterial system.

-27-

27. A kit of Claim 22 wherein said treatment of atherosclerosis causes the regression of atherosclerotic plaques.
28. A kit of Claim 27 wherein said regression of atherosclerotic plaques occurs in coronary arteries.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/23480

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/20 A61K31/40 A61K31/365 A61K31/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 93 13801 A (PROCTER & GAMBLE) 22 July 1993</p> <p>see page 2, paragraph 6 see page 5, paragraph 2 see page 8, paragraph 3 see page 13, paragraph 3 see page 17; examples IB,C,D,II see examples III,VI</p> <p>----</p> <p style="text-align: center;">-/-</p>	<p>1-4, 6-10, 12-17, 19, 22-28</p>



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 May 1999

Date of mailing of the international search report

01/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Kanbier, D

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23480

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GLUECK ET AL: "Gemfibrozil-Lovastatin Therapy for Primary Hyperlipoproteinemia" THE AMERICAN JOURNAL OF CARDIOLOGY, vol. 70, no. 1, 1 July 1992, pages 1-9, XP002103067	1-3, 6, 7, 12, 13, 15, 16, 19-28
Y	see page 1, right-hand column - page 2; figures; tables	1, 4-6, 8, 9, 11, 12, 14, 15, 17-28
X	---	
X	HAAG ET AL: "Lovastatin Inhibits Receptor-Stimulated Ca++-Influx in Retinoic Acid Differentiated U937 and HL-60 Cells" CELLULAR SIGNALLING, vol. 6, no. 7, 1994, pages 835-742, XP002103068	1-4
	see page 741, right-hand column - page 742, left-hand column; figures 1-3; table 1	
X	---	
A	RAMIRES ET AL: "Effect of Gemfibrozil versus Lovastatin on Increased Serum Lipoprotein(a) Levels of Patients with Hypercholesterolemia" INTERNATIONAL JOURNAL OF CARDIOLOGY, vol. 48, no. 2, 1995, pages 115-120, XP002103069	1, 6, 12, 15
	see page 117, right-hand column, paragraph 1	
	see page 118, right-hand column, paragraph 2	
X	---	
EP 0 738 510 A (OREAL) 23 October 1996		1-4, 15-17
A	see page 3, line 23-25; claims 1, 4, 6, 11-13	6-10, 12-14
	see page 3, line 37-38	
X	---	
WO 97 14403 A (MARY KAY INC) 24 April 1997		1-4, 15-17
A	see page 66, line 4-10; claim 1	6-10, 12-14
X	---	
DIMITROULAKOS ET AL: "HMG-CoA Reductase Mediates the Biological Effects of Retinoic Acid on Human Neuroblastoma Cells: Lovastatin Specifically Targets P-Glycoprotein-Expressing Cells" NATURE MEDICINE, vol. 2, no. 3, March 1996, pages 326-333, XP002103070	1-4, 6-8, 12-14	
A	see page 329-330; figure 3D	19

	-/-	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/23480

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RAMHARACK ET AL: "Retinoids Inhibit Primary Cynomolgus Monkey Hepatocyte Lipoprotein(a) Levels" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 238, no. 1, 8 September 1997, pages 48-52, XP002103071 see page 48, right-hand column, paragraph 2 see page 50, right-hand column, paragraph 1 see page 51, right-hand column, paragraph 2 -----	1,4-6,8, 9,11,12, 14,15, 17-28
A	WO 93 16690 A (WARNER LAMBERT CO) 2 September 1993 -----	1
A	KRAUSE ET AL: "Emerging Therapies in Atherosclerosis" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 4/5, 1995, pages 353-387, XP002103072 see page 357, left-hand column, paragraph 1 see page 357, left-hand column, paragraph 4 - page 358, right-hand column, paragraph 1 see page 365, right-hand column, paragraph 3 - page 369, right-hand column, paragraph 2 -----	1-3,6,7, 9,10,12, 13,19, 22-28
2		

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 23480

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 1-28 because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: - because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210
3. Claims Nos.: - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The term "Lp(a) inhibitor" in claims 1, 6, 12, 15 is vague and indefinite; the scope of these claims is therefore not completely clear. Only the general concept and the compounds mentioned in claims 4, 5, 8, 9, 11, 14, 17 and 18, and in the example (clinical trial) have been searched. The same goes for the term "statin" in claims 1, 6, 9, 12, 15 and the compounds mentioned in claims 2, 3, 7, 10, 13, 16. It is to be noted that the "Lp(a) inhibitors" other than retinoids, described on pages 2-5 of the description, have NOT been searched due to the above.

INTE TIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/23480

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9313801	A 22-07-1993	AU 3473193 A	MX 9300240 A		03-08-1993 29-07-1994
EP 0738510	A 23-10-1996	CA 2174598 A	JP 8291047 A		21-10-1996 05-11-1996
		US 5733558 A			31-03-1998
WO 9714403	A 24-04-1997	US 5720963 A	AU 7461996 A		24-02-1998 07-05-1997
		CA 2234975 A	CN 1202817 A		24-04-1997 23-12-1998
		EP 0855904 A			05-08-1998
WO 9316690	A 02-09-1993	AU 3315397 A	AU 4275793 A		30-10-1997 13-09-1993
		CA 2129732 A	EP 0627917 A		02-09-1993 14-12-1994
		JP 7505145 T	MX 9301014 A		08-06-1995 01-09-1993
		US 5633285 A			27-05-1997
		ZA 9301297 A			27-06-1994

